1382887

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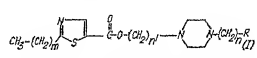
(19)

(54) THIAZOLE-5-CARBOXLIC ACID ESTERS

(71) We, ROUSSEL UCLAF, a French Body Corporate of 35, Boulevard des Invalides, Paris 7e, France, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention relates to new esters of 2 - alkyl thiazole - 5 - carboxylic acid and a process for preparing these compounds.

According to the present invention we provide compounds of general formula I:



(I)

(in which n represents 0, 1, 2, 3, 4 or 5, n' represents 1, 2, 3, 4, or 5, m represents 0, 1, 2, 3, 4 or 5 and R represents a substituted or unsubstituted phenyl radical of general formula:

where X_1 and X_2, which may be the same or different, each represent a hydrogen, chlorine, bromine or iodine atom, an alkyl radical containing from 1 to 6 carbon atoms, an alkoxy radical containing 1 to 6 carbon atoms which may, if desired, be substituted by a diethylamino group or by up to 3 fluorine atoms, or a tri - halogenomethyl group, or R represents a heterocyclic ring containing a maximum of 6 nuclear atoms and containing one or more nuclear heteroatoms) and salts of these compounds with a mineral or organic acid.

In the compounds of formula I, X_1 and X_2 may more particularly represent a methyl, ethyl, propyl, isopropyl, *n* - butyl, sec - butyl or tert - butyl radical, or a methoxy, ethoxy, propoxy, isopropoxy, n - butoxy, sec - butoxy, tert - butoxy, diethylaminoethoxy or trifluoroethoxy radical. The heterocyclic radical R may more particularly represent a pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiapyranyl, oxazinyl or thienyl radical, the value of the m factor is preferably 0, 1 or 2.

The compounds of the invention possess valuable adrenolytic and peripheral vasodilatatory activity and are thus useful in treating hypertension, in improving cerebral circulation and in treating migraine.

Particular compounds according to the present invention of particular interest in view of this activity are:

ω[4' - (*o* - methoxyphenyl) - 1' - piperazino] - butyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride,

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β - [4′ - (o,o′ - dimethylphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate and its monohydrochloride,
β - (4′ - benzyl - 1′ - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride,
β - (4′ - p - tolyl - 1′ - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride,
β - (4′ - o - tolyl - 1′ - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate and its hydrochloride,
β - [4′ - (p - methoxyphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride,
β - [4′ - (o - methoxyphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate, its maleate and its dihydrochloride,
β - (4′ - α - pyridyl - 1′ - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate and its maleate,
β - (4′ - phenyl - 1′ - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride,
β - [4′ - (o - chlorophenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate and its monohydrochloride,
β - [4′ - (m - trifluoromethylphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate and its monohydrochloride,
β - [4′ - (o - ethoxyphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate and its maleate,
β - [4′ - (o - methoxyphenyl) - 1′ - piperazino] - ethyl 2 - methyl - thiazole - 5 - carboxylate and its maleate, and
β - [4′ - (o - methoxyphenyl) - piperazino] - ethyl 2 - butyl - thiazole - 5 - carboxylate and its oxalate.

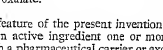
According to a further feature of the present invention we provide pharmaceutical compositions containing as an active ingredient one or more compounds of formula I as defined above together with a pharmaceutical carrier or excipient.

The compositions according to the present invention may be administered by the oral, perlingual, transcutaneous or rectal route. They can take the form, for example, of injectable solutions or suspensions dispensed for example, in ampoules or in multi-dose phials; plain or coated tablets; sublingual tablets and suppositories.

The daily dose can range, for example, between 10 and 100 mg. per day for the adult using the parenteral route, and between 100 and 500 mg. using the oral or rectal route.

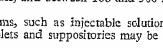
The pharmaceutical forms, such as injectable solutions or suspensions, plain or coated tablets, sublingual tablets and suppositories may be formulated in conventional manner.

According to a further feature of the present invention we provide a process for preparing compounds of the formula I, as well as the salts of these compounds with mineral or organic acids, wherein a 2 - alkylthiazole - 5 - carboxylic acid of general formula



(II)

in which m has the aforesaid meaning, or a functional derivative of this acid is reacted with an alcohol of general formula



(III)

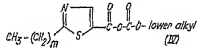
in which n′, n and R have the aforesaid meanings, and the resulting ester of general formula I is optionally converted into a salt.

The free 2 - alkylthiazole - 5 - carboxylic acid of formula II may be used and in this case it is desirable to effect the reaction in the presence of an acid catalyst, such as paratoluene sulphonic acid or hydrochloric acid, and to remove the water formed as the reaction continues.

One can also use a functional derivative, for example the halide, e.g. the chloride,

or the anhydride of the acid of formula II, preferably operating in the presence of a tertiary base, such as triethylamine or pyridine. The anhydride of the 2 - alkylthiazole - 5 - carboxylic acid can be conveniently obtained by reacting the corresponding acid with a dehydrating reagent such as dicyclohexyl carbodiimide.

To carry out esterification one can also use a mixed anhydride of the acid of formula II. This anhydride may be obtained by reacting a tertiary base with the acid, then subjecting the resulting salt to the action of a lower alkyl chloroformate, e.g. methyl or ethyl chloroformate, to obtain the mixed anhydride of general formula



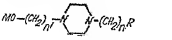
(III)

(where m is as defined above) which one reacts with the alcohol of formula III. The tertiary base which one reacts with the acid is preferably triethylamine or pyridine.

The salification of the acid II by the tertiary amine, the reaction with chloroformate and the reaction of anhydride with the alcohol are all conveniently effected in an organic solvent such as acetone.

Condensation of the mixed anhydride IV with alcohol III, is preferably carried out in an acetone medium as, together with the desired ester I, it tends to form a lower alkyl hemicarbonate, which is immediately decomposed into carbon dioxide and the corresponding alcohol.

The esterification can also be carried out by reacting the acid or one of its functional derivatives with an alcoholate of formula:



in which M represents an alkali - metal atom and n' and n are as defined above.

The optional conversion of the amine functions or the ester I piperazine ring into salt form, may for example be effected by the action of a suitable acid with ester I. This salt formation may be carried out in an organic solvent such as methanol, ethanol, isopropanol, acetone or ether.

The piperazino alkanols used are described in general in the literature.

4 - benzylpiperazino - ethanol can be obtained according to the process described in Naturwissenschaften *53* (16) 405 (1966).

4 - *α* - pyridylpiperazino - ethanol can be obtained according to the process described in U.S. Patent 2,562,036.

4 - *o* - tolylpiperazino - ethanol is described by C. B. Pollard and T. H. Wicker J. Am. Chem. Soc. *76* 1853 (1954).

4 - (*p* - methoxyphenyl) - piperazino - ethanol is described in British Patent 889,223.

4 - (*o* - methoxyphenyl) - piperazino - butanol is described in U.S. Patent 2,922,788.

4 - *p* - tolylpiperazino - ethanol and 4 - (*o* - chlorophenyl) - piperazino - ethanol are both described by C. B. Pollard and T. H. Wicker J. Am. Chem. Soc. *76* 1853 (1954).

4 - (o - Ethoxyphenyl) - piperazino - ethanol, 4 - (2',5' - dimethylphenyl)-piperazino ethanol, and 4 - (3 - trifluoromethylphenyl)piperazino - ethanol can be prepared by the action of ethylene oxide on the corresponding substituted piperazines. The preparations for these 3 compounds which are not described in the literature, are given in the experimental section.

The other alcohols of general formula III can be prepared by the known methods, more particularly, by those described in the references quoted above

2 - alkylthiazole - 5 - carboxylic acids are obtained by the process described in French Patent No. 2,047,876.

The following examples illustrate the invention without limiting it.

Preparations:

A) 2 - [4 - (*o,o'* - dimethylphenyl) - piperazino] - ethanol:

One adds at −15°C 43 c.c. of a methanolic solution of ethylene oxide with a titre of 200 g./litre to a solution of 14.3 g. of N - (2,6 - dimethylphenyl)piperazine in

38 c.c. of methanol. The mixture is allowed to stand for 90 hours, and then one removes the solvent by distillation under reduced pressure, rectifies the residue and obtains 14.67 g. of 2 - [4 - (*o,o'* - dimethylphenyl) - piperazino] - ethanol, b.p.= 146°C under 0.05 mm. of mercury.

B) 2 - [4 - (*m* - trifluoromethylphenyl) - piperazino] - ethanol:
In a similar way to that of the preceding Preparation, starting with 17.3 g. of N - (*m* - trifluoromethylphenyl)piperazine, one obtains 15.8 g. of 2 - [4 - (*m* - trifluoromethylphenyl) - piperazino] - ethanol, b.p.=143°C, under 0.1 mm. of mercury.

C) 2 - [4 - (*o* - ethoxyphenyl) - piperazino] - ethanol:
In a similar way to that in Preparation A), starting with 10.3 g. of N - (*o* - ethoxyphenyl) - piperazine, one obtains 7.9 g. of 2 - [4 - (*o* - ethoxyphenyl) - piperazino] - ethanol, b.p.=148°C, under 0.1 mm. of mercury.

Example I

β - (4' - phenyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate dihydrochloride

One puts 10.27 g. of 2 - propylthiazole - 5 - carboxylic acid into suspension in 70 c.c. of acetone, adds a solution of 9.10 g. of triethylamine in 20 c.c. of acetone, then over 20 minutes and maintaining the temperature between +6° and +8°C adds a solution of 8.14 g. of ethyl chloroformate in 30 c.c. of acetone; one lets the reaction mixture come back to ambient temperature, suction-filters and washes the precipitate with acetone; one cools the combined filtrates to +8°C, adds a solution of 12.37 g. of 4 - phenyl 1' - piperazino ethanol (obtained according to the process described in J. Med. Chem. *6* 133—135, 1963) in 30 c.c. of acetone, leaves the reactants in contact for one night and evaporates off the acetone; one takes the oily residue up with 150 c.c. of ether and 10 c.c. of water, washes the ethereal phase with an aqueous solution containing 20% of potassium carbonate, to bring to pH 10, decants the organic phase and re-extracts the aqueous phases with ether; one washes the combined ethereal phases with water, dries on magnesium sulphate, treats with active charcoal, filters and evaporates off the solvent; one obtains 17.5 g. of *β* - (4' - phenyl 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate; one dissolves 17.24 g. of the base obtained above in 30 c.c. of ethanol, adds the stoichiometric quantity of a 4.29 N solution of hydrochloric acid in ethanol, suction-filters and dries the precipitate. One purifies the product by recrystallization from isopropanol and obtains 10 g. of *β* - (4' - phenyl 1' - piperazino) ethyl 2 - propyl thiazole 5 - carboxylate dihydrochloride, in the form of colourless crystals, soluble in chloroform, fairly soluble in water and methanol, slightly soluble in ethanol, insoluble in ether, acetone and benzene, melting at 160°C.

Analysis: $C_{19}H_{23}N_3O_2S$, $2HCl$ = 432.41

	C%	H%	Cl%	N%	S%
Calculated:	52.77	6.29	16.4	9.72	7.41
Found:	52.5	6.1	16.3	9.5	7.6

U.V. Spectrum ethanol:
Max. at 245 nm $E_{1\,cm}^{1\%}$ = 502

I.R. Spectrum —KBr:
Peaks at 3000, 2960, 2400, 1720, 1600 and 1500 cm^{-1}

Example II

β - [4' - (*o* - methoxyphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate dihydrochloride

One puts 10.3 g. of 2 - propylthiazole - 5 - carboxylic acid into suspension in 70 c.c. of acetone, adds a solution of 9.1 g. of triethylamine in 20 c.c. of acetone, cools the mixture to +6°C and adds a solution of 8.1 g. of ethyl chloroformate in 35 c.c. of acetone under agitation and maintaining the temperature at +6°C; one lets the mixture come back to ambient temperature and continues agitation for 30 minutes; one filters and washes the precipitate with acetone; one cools the combined acetonic phases to +8°C, adds a solution of 14.2 g. of 4 - (*o* - methoxyphenyl) - piperazino - ethanol (obtained according to the process described in Chem. Abstr., 1958, 52 p. 20216c) in 70 c.c. of acetone under agitation and maintaining the temperature at +8°C, one lets the solution come back to ambient temperature, leaves the solution to stand for 48 hours then evaporates it to dryness; one takes up the oily residue with 150 c.c. of ether, washes the ethereal phase with water, then with an aqueous solution containing

20% potassium carbonate and finally with water till the washing waters are neutral; one dries the ethereal phase on magnesium sulphate, treats with active charcoal, filters and evaporates to dryness; one obtains 16.9 g. of β - 4' - (o - methoxyphenyl) - 1' - piperazino ethyl 2 - propyl - thiazole - 5 - carboxylate.

One dissolves the 16.9 g. of base in 170 c.c. of ethanol, adds 20 c.c. of a 4.3 N solution of hydrochloric acid in ethanol, filters, washes the precipitate with ethanol and dries; by recrystallization from ethanol one obtains 9.1 c.c. of β - [4' - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate dihydrochloride, in the form of colourless crystals, soluble in water and methanol, insoluble in ether, benzene and acetone, melting at 170°C.

Analysis: $C_{24}H_{32}Cl_2N_3O_3S = 462.43$

	N%	S%	Cl%
Calculated:	9.08	6.93	15.33
Found:	8.62—8.63	6.58—6.61	15.01—14.94

I.R. Spectrum —KBr:
Bands at 3000, 2400, 1700, 1600, 1420, 1280, 1100, 1010, 750 and 630 cm^{-1}

U.V. Spectrum ethanol:
Max. at 246 nm $E_{1\ cm}^{1\%} = 350$

Obtaining the maleate:

To 1.19 g. of maleic acid in solution in 150 c.c. of ether, one adds 4 g. of β - [4' - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate in solution in 50 c.c. of ether, leaves the mixture to stand for 2 hours 30 minutes, isolates the precipitate formed by suction filtering, washes it with ether, crystallizes it in ethyl acetate and obtains 4.4 g. of β - [4' - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate maleate, m.p.=133°C.

Analysis: $C_{24}H_{32}N_3O_7S = 505.595$

	C%	H%	N%	S%
Calculated:	57.02	6.18	8.31	6.34
Found:	56.8	6.0	8.0	6.4

Example III

β - [4' - (o - chlorophenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate hydrochloride

One adds a solution of 7.9 g. of triethylamine in 25 c.c. of acetone to a suspension of 8.9 g. of 2 - propylthiazole - 5 - carboxylic acid in 60 c.c. of acetone; one cools to +6°C, over 20 minutes adds a solution of 6.8 g. of ethyl chloroformate in 25 c.c. of acetone under agitation and maintaining the temperature between +6° and +8°C; one lets the reaction mixture come back to ambient temperature, filters and washes the precipitate with acetone; one cools the combined filtrates to +6°C, adds a solution of 9.6 g. of 4' - (o - chlorophenyl) - piperazino - ethanol in 40 c.c. of acetone, under agitation and maintaining the temperature between 8° and 10°C; one lets the solution come back to ambient temperature, agitates the solution for 3 hours and leaves in contact for 12 hours; one evaporates off the acetone, takes up the residue with 50 c.c. of ether and 10 c.c. of water, washes the ethereal phase with an aqueous solution containing 10% potassium carbonate till the washing waters are neutral, then with water and dries on magnesium sulphate; one treats the dried ethereal phase with active charcoal, filters and evaporates to dryness; one obtains 14.6 g. of β - [4' - (o - chlorophenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate.

One dissolves the 14.6 g. of base obtained above in 250 c.c. of ether and adds 8.60 c.c. of a 4.29 N ethanolic solution of hydrochloric acid; one filters the mixture, washes the precipitate with ether and dries; and obtains 13.8 g. β - [4' - (o - chlorophenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate hydrochloride.

For the analysis one recrystallizes the compound from isopropanol; the melting point remains unchanged.

The product takes the form of colourless crystals, soluble in water, methanol and ethanol, insoluble in ether, melting at 145°C.

Analysis: $C_{24}H_{32}Cl_2N_3O_3S = 430.39$

	C%	H%	Cl%	N%	S%
Calculated:	53.02	5.85	16.48	9.76	7.45
Found:	52.8	5.8	16.5	9.6	7.4

U.V. Spectrum ethanol:
Max. at 250 nm $E_{1\ cm}^{1\%}=400$

I.R. Spectrum —KBr:
Bands at 3080, 2960, 2920, 2880, 2840, 2680, 2500, 1700, 1580, 1440, 1280, 1100, 1010 and 750 cm^{-1}.

Example IV

β - (4' - *p* - tolyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate dihydrochloride

One puts 9.8 g. of 2 - propylthiazole - 5 - carboxylic acid into suspension in 70 c.c. of acetone, adds a solution of 6.4 g. of triethylamine in 20 c.c. of acetone and cools to 6°C; one adds a solution of 6.5 g. of ethyl chloroformate in 30 c.c. of acetone under agitation and maintaining the temperature between 6° and 8°C; one brings back the mixture to ambient temperature, agitates for 40 minutes, filters and rinses the filter with acetone; one cools the combined filtrates to 8°C, adds a solution of 11 g. of 4 - *p* - tolyl piperazino ethanol (obtained according to the process described in J. Am. Chem. Soc. 76, 1854, 1954) in 40 c.c. of acetone, maintaining the temperature between 8° and 10°C and leaves the mixture in contact for 48 hours; one evaporates off the acetone, takes up the residue with 200 c.c. of ether and 20 c.c. of water, washes the ethereal phase with an aqueous solution containing 20% potassium carbonate, then with water till pH is neutral, dries on magnesium sulphate, treats with active charcoal, filters and evaporates off the ether; one takes up the residue with 5 c.c. of petroleum ether, recrystallizes the precipitate from isopropyl ether and obtains 7.8 g. of β - (4' - *p* - tolyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate, in the form of colourless crystals, melting at 50°C.

Analysis: $C_{21}H_{31}N_3SO_2$=373.50

Calculated:	N% 11.25	S% 8.58	
Found:	11.11—11.03	8.67—8.67	

One dissolves the 7.8 g. of compound obtained above in 80 c.c. of ethanol, adds 9.8 c.c. of a 4.29 N solution of hydrochloric acid in ethanol, filters and recrystallizes the precipitate from ethanol; one obtains 7.3 g. of β - (4' - *p* - tolyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate dihydrochloride, in the form of colourless crystals, soluble in water, ethanol, methanol and chloroform, insoluble in benzene and ether, melting at 183°C.

Analysis: $C_{21}H_{31}N_3SO2HCl$=446.43

Calculated:	C% 53.80	H% 6.55	Cl% 15.89	N% 9.41	S% 7.18
Found:	53.5	6.5	16.0	9.6	6.8

U.V. Spectrum ethanol:
Max. at 247 nm $E_{1\ cm}^{1\%}=488$

I.R. Spectrum —KBr:
Presence of N° at 2440 cm^{-1}, of C=O at 1720 cm^{-1}, and of C=O atomatic ester at 1100 cm^{-1}.

Example V

β - (4' - benzyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate dihydrochloride

One puts 8.9 g. of 2 - propyl - thiazole - 5 - carboxylic acid into suspension in 60 c.c. of acetone, adds a solution of 7.9 g. of triethylamine in 25 c.c. of acetone and cools to 6°C; one adds a solution of 6.8 g. of ethyl chloroformate in 25 c.c. of acetone under agitation and maintaining the temperature between 6° and 8°C; one brings back the mixture to ambient temperature, agitates for 40 minutes, filters and rinses the filter with acetone; one adds to the combined filtrates a solution of 8.8 g. of 4 - benzyl - piperazino - ethanol (obtained according to the process described in Chem. Abstr. 65, 16970f, 1966) in 25 c.c. of acetone, maintaining the temperature between 8° and 10°C and leaves the mixture in contact for 18 hours; one evaporates off the acetone, takes up the residue with 100 c.c. of ether and 10 c.c. of water, washes the ethereal phase with an aqueous solution containing 10% potassium carbonate, then with water, dries on magnesium sulphate, treats with active charcoal, filters and evaporates off the ether. After reprecipitation from an acetone-water mixture and washing the crystals

with ethanol containing 10% water, one obtains 6.4 g. of β - (4′ - benzyl - 1′ - piperazino - ethyl 2 - propyl - thiazole - 5 - carboxylate, melting at 48°C.

Analysis: $C_{29}H_{37}N_3SO_2$=373.50
Calculated: S% 8.58
Found: 8.57—8.54

One dissolves the 6.4 g. of the compound obtained above in 35 c.c. of ethanol, adds 8 c.c. of a 4.29 N solution of hydrochloric acid in ethanol and filters; by recrystallization from ethanol, one obtains 5.3 g. of β - (4′ - benzyl - 1′ - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate dihydrochloride, in the form of colourless crystals, soluble in water, slightly soluble in chloroform, insoluble in ether and benzene, melting at 208°C.

Analysis: $C_{29}H_{37}N_3SO_2$2HCl=446.43
Calculated: C% 53.80 H% 6.55 Cl% 15.89 N% 9.41 S% 7.18
Found: 53.8 6.3 15.8 9.3 6.9

U.V. Spectrum ethanol:
Max. at 256 nm $E_{1\ cm}^{1\%}$=261

I.R. Spectrum:
Presence of N⁺ carbonyl at 1715 cm^{-1}, of mono-substituted aromatic structure at 750 and 699 cm^{-1} and of thiazole at 1673 and 1653 cm^{-1}.

Example VI

ω - [4′ - (o - methoxyphenyl) - 1′ - piperazino] - butyl 2 - propyl - thiazole - 5 - carboxylate dihydrochloride

One dissolves the 11.3 g. of base in 14 c.c. of ethanol, adds 12.6 c.c. of a 4.29 N 60 c.c. of acetone, adds a solution of 4.5 g. of triethylamine in 20 c.c. of acetone, cools to +6°C and adds a solution of 4.6 g. of ethyl chloroformate in 25 c.c. of acetone under agitation and maintaining the temperature between +6° and +8°C; one brings the mixture back to ambient temperature, agitates for 1 hour, filters and rinses the filter with acetone; one cools the combined filtrates to +8°C, adds a solution of 9.3 g. of 4 - (o - methoxyphenyl) - piperazino - butanol (prepared according to the process described in U.S. Patent No. 2,922,788) in 30 c.c. of acetone, maintaining the temperature between +8° and 10°C and leaves in contact for 48 hours; one evaporates the mixture to dryness, takes up the residue with 200 c.c. of ether and 20 c.c. of water, separates the ethereal phase, washes it with an aqueous solution containing 20% potassium carbonate, then with water, treats with active charcoal, filters, dries on magnesium sulphate and evaporates to dryness; one obtains 11.3 g. of ω - [4′ - (o - methoxyphenyl) - 1′ - piperazino] - butyl - 2 - propyl - thiazole - 5 - carboxylate.

One dissolves the 11.3 g. of base in 14 c.c. of ethanol, adds 12.6 c.c. of a 4.29 N ethanolic solution of hydrochloric acid and filters; one recrystallizes the precipitate from ethanol and obtains 6.6 g. of ω - [4′ - (o - methoxyphenyl) - 1′ - piperazino] - butyl - 2 - propyl - thiazole - 5 - carboxylate dihydrochloride in the form of colourless crystals, soluble in water, methanol, ethanol and chloroform, insoluble in ether and benzene, melting at 160°C.

Analysis: $C_{33}H_{41}N_3O_3S2HCl$=490.49
Calculated: C% 53.86 H% 6.78 Cl% 14.46 N% 8.57 S% 6.54
Found: 54.1 6.8 14.2 8.4 6.2

U.V. Spectrum ethanol:
Max. at 243 nm $E_{1\ cm}^{1\%}$=340

I.R. Spectrum —KBr:
Presence of N⁺ at 2380 cm^{-1}, of C=O at 1700 cm^{-1} and of C=N-thiazole at 1600 cm^{-1}.

Example VII

β - [4′ - (o,o′ - dimethylphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate hydrochloride

One puts 9.85 g. of 2 - propylthiazole - 5 - carboxylic acid into suspension in 70 c.c. of acetone, adds a solution of 6.4 g. of triethylamine in 20 c.c. of acetone, cools to

+6°C and adds a solution of 6.55 g. of ethyl chloroformate in 30 c.c. of acetone under agitation and maintaining the temperature between +6° and +8°C; one allows the mixture to come back to ambient temperature, agitates for 1 hour, filters and washes the filter with acetone; one cools the combined filtrates to +6°, +8°C, adds a solution of 11.72 g. of 4' - (*o,o'* - dimethylphenyl) - piperazino - ethanol (obtained according to the process described in part A of the Preparations) in 30 c.c. of acetone under agitation, agitates for 30 minutes and leaves in contact for 84 hours; one evaporates the mixture to dryness under vacuum, takes up the residue with 200 c.c. of ether and 20 c.c. of water, separates the ethereal phase, washes it with an aqueous solution containing 10% potassium carbonate, then with water, treats with active charcoal, filters, dries on magnesium sulphate, filters and evaporates to dryness under vacuum; one obtains 19.17 g. of β - [4' - (*o,o'* - dimethylphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate.

One triturates 19 g. of base with 103 c.c. of N hydrochloric acid, suction-filters, makes the residue into a paste with ether, suction-filters, washes the residue with acetone and crystallizes it in water: one obtains 6.53 g. of β - [4' - (*o,o'* - dimethylphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate hydrochloride in the form of colourless crystals, soluble in methanol, ethanol, chloroform and water, insoluble in benzene and ether, melting at 195°C.

Analysis: $C_{21}H_{30}ClN_3O_2S$ = 424.00

	C%	H%	Cl%	N%	S%
Calculated:	59.48	7.13	8.36	9.81	7.56
Found:	59.6	7.1	8.5	9.6	7.7

I.R. Spectrum – KBr:
Presence of

at 2940 cm^{-1}, of N^- at 2540 cm^{-2}, of C=O ester at 1700 cm^{-1} and of

at 1290 at 1100 cm^{-1}.

Example VIII

β - [4' - (*m* - trifluoromethylphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate hydrochloride

Operating as in example VII, starting with 9.85 g. of 2 - propylthiazole 5 - carboxylic acid, 6.4 g. of triethylamine, 6.55 g. of ethyl chloroformate and 13.72 g. of 4' - (*m* - trifluoromethylphenyl) - piperazino - ethanol (obtained according to the process described in part B of the preparation), one obtains 21.45 g. of β - [4' - (*m* - trifluoromethylphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate. By reacting 104 c.c. of N hydrochloric acid with 21.2 g. of base, one obtains 6.7 g. of β - [4' - (*m* - trifluoromethylphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate hydrochloride.

The compound takes the form of colourless crystals, soluble in water, methanol and ethanol, insoluble in ether and benzene, melting at 202°C.

Analysis: $C_{25}H_{30}ClF_3N_4O_2S$ = 463.95

	C%	H%	Cl%	F%	N%	S%
Calculated:	51.77	5.43	7.64	12.28	9.06	6.91
Found:	52.0	5.5	7.7	12.1	8.9	6.8

I.R. Spectrum – KBr:
Presence of

at 2940 and 2900 cm^{-1}, of N^+ at 2570 cm^{-1}, of C=O ester at 1710 cm^{-1}, of C=N-thiazole at 1600 cm^{-1}, of CF_3 at 1310, 1160 and 750 cm^{-1}, of

ester at 1280 and 1110 cm^{-1}.

Example IX

β - 4' - (o - tolyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate hydrochloride

Operating as in example VII, starting with 8.8 g. of 2 - propylthiazole - 5 - carboxylic acid, 5.8 g. of triethylamine, 5.9 g. of ethyl chloroformate and 9.9 g. of 4 - (o - tolyl) - piperazino - ethanol, one obtains 15.5 g. of β - (4' - o - tolyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate. Reacting 85 c.c. of N hydrochloric acid with the 15.5 g. of base, one obtains 9.9 g. of β - (4' - o - tolyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate ethanol and chloroform, slightly soluble in water, insoluble in ether and benzene, melting at 198°C.

Analysis: $C_{20}H_{27}N_3O_2S$, HCl=409.97

	C%	H%	Cl%	N%	S%
Calculated:	58.59	6.88	8.65	10.25	7.82
Found:	58.8	6.5	8.9	10.4	7.7

U.V. Spectrum ethanol:
Max. at 247 nm $E_{1\ cm}^{1\%}$=338

I.R. Spectrum —KBr:
Presence of N^+ at 2560 cm^{-1}, of C=O ester at 1720 cm^{-1} and of C=N-thiazole at 1600 cm^{-1}.

The 4 - (o - tolyl) - piperazino - ethanol is obtained according to the process described by Pollard *et al*, J. Am. Chem. Soc. *76*, 1853—*5*, 1954.

Example X

β - [4' - (p - methoxyphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride

Operating as in example VII, starting with 8.8 g. of 2 - propylthiazole - 5 - carboxylic acid, 5.8 g. of triethylamine, 5.9 g. of ethyl chloroformate and 10.6 g. of 4 - (p - methoxyphenyl) - piperazino - ethanol, one obtains 11.4 g. of β - [4' - (p - methoxyphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate in the form of colourless crystals, soluble in methanol, ether, benzene, acetone and chloroform, insoluble in water, melting at 77°C.

Analysis: $C_{20}H_{27}N_3O_3S$=389.50

	S%	N%
Calculated:	8.23	10.78
Found:	7.91—7.89	10.65—10.62

The 4 - (p - methoxyphenyl) - piperazino - ethanol is obtained according to the process described in British Patent No. 889,223 (C.A., 1962, *57*, 13778a)

By reacting 15 c.c. of a 3.15 N ethanolic solution of hydrochloric acid with 9.2 of base, one obtains 5.9 g. of β - [4' - (p - methoxyphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylic dihydrochloride, in the form of colourless crystals, soluble in water, methanol and chloroform, slightly soluble in ethanol, insoluble in ether and benzene, melting at 168°C.

Analysis: $C_{20}H_{27}N_3O_3S$, 2HCl=462.43

	C%	H%	Cl%	N%	S%
Calculated:	51.94	6.32	15.53	9.08	6.93
Found:	52.0	6.0	15.3	9.3	6.6

U.V. Spectrum ethanol:
Max. at 242 nm $E_{1\ cm}^{1\%}$=465

I.R. Spectrum —KBr:
Presence of N^+ at 2400 cm^{-1}, of C=O ester at 1720 cm^{-1} and of C=N-triazole at 1620 cm^{-1}.

Example XI

β - (4' - α - pyridyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate and its maleate

Operating as in example VII, starting with 9.8 g. of 2 - propylthiazole - 5 - carboxylic acid, 6.4 g. of triethylamine, 6.5 g. of ethyl chloroformate and 102 g. of 4 - (α' - pyridyl) - piperazino - ethanol, one obtains 5.4 g. of β - (4' - α - pyridyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate, in the form of colourless crystals soluble in ether, ethanol, benzene and acetone, insoluble in water, melting at 56°C.

Analysis: $C_{19}H_{24}O_2S$=360.47

	C%	H%	N%	S%
Calculated:	59.97	6.71	15.54	8.90
Found:	59.7	6.6	15.5	8.7

The 4 - (α' - pyridyl) - piperazino - ethanol is obtained according to the process described in U.S. Patent No. 2,562,036.

By reacting a solution of 1.45 g. of maleic acid in 100 c.c. of ether, with a solution of 4.5 g. of β - (4' - α - pyridyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate in 50 c.c. of ether, one obtains 4 g. of maleate in the form of colourless crystals, soluble in methanol, slightly soluble in water and ethanol, insoluble in ether, melting at 154°C.

Analysis: $C_{23}H_{28}N_4O_6S$=476.54

	C%	H%	N%	S%
Calculated:	55.45	5.92	11.76	6.73
Found:	55.4	5.8	11.5	6.4

I.R. Spectrum —KBr:
Presence of C=O ester at 1720 cm^{-1} and C=N thiazole at 1600 cm^{-1}.

Example XII

β - [4' - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - methyl - thiazole - 5 - carboxylate and its maleate

To the suspension of 8.59 g. of 2 - methyl - thiazole - 5 - carboxylic acid (compound described by Rublew Ann. 259, 271) in 60 c.c. of acetone, one adds 7.28 g. of triethylamine in 30 c.c. of acetone, then one adds 7.16 g. of ethyl chloroformate in solution in 30 c.c. of acetone over 30 minutes at +5°C, agitates for 1 hour at ambient temperature, removes, by filtering, the triethylamine hydrochloride formed, adds 14.1 g. of 4 - (o - methoxyphenyl) - piperazino - ethanol to the filtrate in 15 minutes, leaves the mixture to stand for 40 hours, removes the acetone by distillation under reduced pressure, dissolves the residue in ether, washes the ethereal solution with potassium carbonate, with water, dries, removes the solvent by distillation, crystallizes the residue in hexane, prepares the dihydrochloride using an ethanolic solution of hydrochloric acid, crystallizes the dihydrochloride in ethanol, isolates the base by adding potassium carbonate and obtains 7.15 g. of β - [4' - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - methyl - thiazole - 5 - carboxylate, m.p.=73°C.

Analysis: $C_{17}H_{23}N_3O_3S$=361.46

	C%	H%	N%	S%
Calculated:	58.81	6.41	11.62	8.87
Found:	60.1	6.3	11.6	8.7

One adds 1.27 g. of maleic acid in solution in 200 c.c. of ether to 4 g. of β - [4' - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - methyl - thiazole - 5 - carboxylate in solution in 145 c.c. of dry ether, isolates the precipitate formed by suction-filtering, crystallizes it in water and obtains 5 g. of β - [4' - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - methyl - thiazole - 5 - carboxylate maleate, m.p.=108—109°C.

Analysis: $C_{23}H_{27}N_3O_7S$=477.53

	C%	H%	N%	S%
Calculated:	55.33	5.70	8.80	6.71
Found:	55.1	5.8	8.7	6.5

Example XIII

β - [4' - (o - ethoxyphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate maleate

In a similar way to that of example VII, starting with 5.5 g. of 2 - propylthiazole -

5 - carboxylic acid, with 7 g. of 4 - (*o* - ethoxyphenyl) - piperazino - ethanol (obtained according to the process described in part C of the preparations), with 3.6 g. of triethylamine and 3.7 g. of ethyl chloroformate; one obtains 4.8 g. of *β* - [4′ - (*o* - ethoxyphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate melting at 42°C.

Analysis: $C_{21}H_{33}N_3O_3S$=403.53

Calculated:	C% 62.50	H% 7.24	N% 10.4	S% 7.95
Found:	62.7	7.3	10.7	7.8

One adds 4.35 g. of *β* - [4′ - (*o* - ethoxyphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate in solution in 20 c.c. of ether to a solution of 1.25 g. of maleic acid in 80 c.c. of ether, isolates the crystals formed by suction-filtering, crystallizes them in isopropanol and obtains 5.2 g. of *β* - [4′ - (*o* - ethoxyphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate maleate m.p.=77°C.

Analysis: $C_{25}H_{33}N_3O_7S$=519.60

Calculated:	C% 57.78	H% 6.40	N% 8.09	S% 6.17
Found:	57.5	6.3	8.2	5.9

Example XIV

β - [4′ - (*o* - methoxyphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate dihydrochloride

a) 2 - propylthiazole 5 - carboxylic acid anhydride:

One introduces a solution of 573.6 g. of dicyclohexyl carbodimide in 4.5 litres of tetrahydrofuran into a solution of 950.76 g. of 2 - propylthiazole - 5 - carboxylic acid in 6 litres of tetrahydrofuran, in 1 hour, agitates the mixture for 3 hours and removes the dicyclohexylurea formed by filtering.

b) esterification:

One adds 655 g. of 4 - (*o* - methoxyphenyl) - piperazino - ethanol in solution in 2.2 litres of tetrahydrofuran to the filtrate previously obtained over a period of 40 minutes, leaves the mixture on one side for 2 days, concentrates to dryness by distillation under reduced pressure, adds ether to the residue, removes a slight amount of insoluble matter by filtering, washes the ethereal solution with an aqueous solution of potassium carbonate, extracts the alkaline washing waters with ether, combines the ethereal solutions, washes them with water, dries them, adds active charcoal, agitates, removes the active charcoal by filtering, concentrates to dryness by distillation under reduced pressure, dissolves the residue in ether, removes a slight amount of insoluble matter by filtering, concentrates to dryness by distillation under reduced pressure, dissolves the residue in ether, removes the insoluble matter again by filtering, concentrates the filtrate almost to dryness by distillation under reduced pressure, isolates the crystals formed by suction-filtering, washes them with petroleum ether (b.p.=65—75°C), dries them and obtains 692 g. of *β* - [4′ - (*o* - methoxyphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate m.p.=59°C.

Beginning with the ethereal filtrate and the petroleum ether, one recovers a second yield of 72 g. of *β* - [4′ - (*o* - methoxyphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate.

c) dihydrochloride:

671 g. of *β* - [4′ - (*o* - methoxyphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate previously obtained are dissolved in 6 litres of ethanol, one adds to this 937 c.c. of 3.67 mol/litre alcohol solution of hydrochloric acid leaves the reaction mixture on one side for 15 hours at 0°C, isolates the crystals formed by suction-filtering, washes them with ether, crystallizes them in ethanol while treating them with active charcoal, and obtains 42 g. of *β* - [4′ - (*o* - methoxyphenyl) - 1′ - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate dihydrochloride m.p.=190°C.

Analysis: $C_{20}H_{31}N_3O_3SCl_2$=462.43

Calculated:	Cl% 15.33	S% 6.92	N% 9.08
Found:	15.51	7.06	9.15

This compound is identical to that obtained by the process of example II.

Example XV

β - [4 - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - butyl - thiazole - 5 - carboxylate oxalate

One mixes 10.66 g. of ethyl 2 - butyl - thiazole - 5 - carboxylate and 11.82 g. of 4 - (o - methoxyphenyl) - piperazino - ethanol under an atmosphere of nitrogen, adds 10.6 g. of sodium methylate, heats the mixture to 140°C, maintains it there for 3 hours 30 minutes, cools, adds ether, leaves the reactants to stand for 1 hour, decants, suction-filters the combined ethereal phases, washes the filtrate with water, dries the filtrate on magnesium sulphate, filters, evaporates to dryness under reduced pressure to obtain an oil which is then chromatographed on silica gel, eluting with a (2 : 1) chloroform - acetone mixture.

One thus isolates 9.9 g. of β - [4' - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - butyl - thiazole - 5 - carboxylate.

Oxalate:

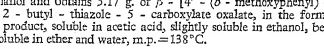
One dissolves 7.7 g. of the base obtained above in 15 c.c. of ethanol, adds a solution of 2.41 g. of oxalic acid in 15 c.c. of ethanol, brings the mixture to boiling point, cools, suction-filters, washes the filter with ethanol, then with ether, recrystallizes the residue from ethanol and obtains 5.17 g. of β - [4' - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - butyl - thiazole - 5 - carboxylate oxalate, in the form of a solid ochre-coloured product, soluble in acetic acid, slightly soluble in ethanol, benzene and acetone, and insoluble in ether and water, m.p. = 138°C.

Analysis: $C_{25}H_{33}N_3O_7S = 493.57$

	C%	H%	N%	S%
Calculated:	55.96	6.33	8.51	6.49
Found:	56.0	6.5	8.5	6.3

WHAT WE CLAIM IS:—

1. Compounds of general formula I:



(I)

(in which n represents 0, 1, 2, 3, 4 or 5, n' represents 1, 2, 3, 4 or 5, m represents 0, 1, 2, 3, 4 or 5 and R represents a substituted or unsubstituted phenyl radical of general formula:

where X_1 and X_2, which may be the same or different, each represents a hydrogen, chlorine, bromine or iodine atom, an alkyl radical containing from 1 to 6 carbon atoms, an alkoxy radical containing from 1 to 6 carbon atoms which may, if desired, be substituted by a diethylamino group or by up to 3 fluorine atoms, or a trihalogenomethyl group, or R represents a heterocyclic ring containing a maximum of 6 nuclear atoms and containing one or more nuclear heteroatoms) and salts of these compounds with a mineral or organic acid.

2. β - [4' - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate, its maleate and its dihydrochloride.

3. β - (4' - phenyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride.

4. β - [4' - (o - chlorophenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate and its hydrochloride.

5. ω - [4' - (o - methoxyphenyl) - 1' - piperazino] - butyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride.

6. β - [4' - (o,o' - dimethylphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate and its monohydrochloride.

7. β - (4' - benzyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride.

8. β - (4' - p - tolyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride.

β - (4' - o - tolyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride.

10. β - [4' - (p - methoxyphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate and its dihydrochloride.

11. β - (4' - α - pyridyl - 1' - piperazino) - ethyl 2 - propyl - thiazole - 5 - carboxylate and its maleate.

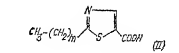
12. β - [4' - (m - trifluoromethylphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate and its monohydrochloride.

13. β - [4' - (o - ethoxyphenyl) - 1' - piperazino] - ethyl 2 - propyl - thiazole - 5 - carboxylate and its maleate.

14. β - [4' - (o - methoxyphenyl) - 1' - piperazino] - ethyl 2 - methyl - thiazole - 5 - carboxylate and its maleate.

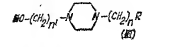
15. β - [4' - (o - methoxyphenyl) - piperazino] - ethyl 2 - butyl - thiazole - 5 - carboxylate and its oxalate.

16. A process for the preparation of compounds as claimed in claim 1 wherein a 2 - alkylthiazole - 5 - carboxylic acid of general formula



(II)

in which m is as defined in claim 1, or a functional derivative thereof, is reacted with an alcohol of general formula



(III)

in which n', n and R are as defined in claim 1, or an alkali metal derivative thereof, and the resulting ester of general formula I is optionally converted into a salt thereof.

17. A process as claimed in claim 16 in which the functional derivative of the acid of formula II is a halide or anhydride.

18. A process as claimed in claim 17 in which the derivative is the chloride or a mixed anhydride.

19. A process as claimed in any of claims 16 to 18 substantially as herein described.

20. A process as claimed in any of claims 16 to 18 substantially as herein described in any of the Examples.

21. Pharmaceutical compositions containing as an active ingredient one or more compounds as claimed in any of claims 1 to 15 together with a pharmaceutical carrier or excipient.

22. Pharmaceutical compositions as claimed in claim 21 substantially as described herein.

For the Applicants,
FRANK B. DEHN & CO.,
Chartered Patent Agents,
Imperial House,
15—19 Kingsway,
London WC2B 6UZ.

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